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Haemodynamic effects of atenolol, labetalol, pindolol and captopril: a comparison in hypertensive patients with special reference to changes in limb blood flow, heart rate and left ventricular function

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1 To compare the haemodynamic effects of secondary characteristics of β-adrenoceptor blockers with an angiotensin converting enzyme inhibitor forty patients with previously untreated mild to moderate hypertension were prescribed either atenolol 50–100 mg day^{-1}, labetalol 200–800 mg day^{-1}, pindolol 10–30 mg day^{-1} or captopril 25–100 mg day^{-1} and observed for 6 months.

2 Over this period:

(a) All four drugs produced similar reductions in blood pressure at rest ($P \leqslant 0.01$) and after exercise ($P \leqslant 0.01$).

(b) All four drugs significantly decreased resting forearm ($P \leqslant 0.01$) and calf blood flow ($P \leqslant 0.01$). They all also caused a significant reduction in the increased calf blood flow following exercise ($P \leqslant 0.01$).

(c) No drug produced a change in resting forearm vascular resistance, while resting calf vascular resistance was decreased by captopril and pindolol, unaltered by labetalol and increased by atenolol. Post-exercise calf vascular resistance was increased by atenolol, labetalol and pindolol but unaltered by captopril.

(d) Although all four drugs produced a fall in resting heart rate this was significantly greater for atenolol and labetalol ($P \leqslant 0.01$). All four treatments however significantly reduced the increase in heart rate following exercise ($P \leqslant 0.01$).

(e) No drug produced any significant change in resting and post-exercise stroke volume/ejection fraction.

3 It is concluded that despite differing modes of action all four drugs reduce limb blood flow. This primarily appears to be a consequence of reduced perfusion pressure associated with limited autoregulation of skeletal muscle circulation. The reduction in arterial vascular resistance produced by captopril and pindolol is inconsistent and does not appear of major benefit in preserving limb blood flow. The reduction in perfusion with the agents studied may in part be related to a fall in cardiac output associated with decreased heart rate. This suggests that captopril may exert antisympathetic activity when used as an antihypertensive agent.

Keywords cardiac output echocardiography limb blood flow perfusion pressure plethysmography vascular resistance

Introduction

The main haemodynamic abnormalities in essential hypertension (W.H.O. Stage I–II) are elevated peripheral vascular resistance and/or raised cardiac output (predominantly due to increased heart rate) (Lund-Johansen, 1980). In 1963, Conway suggested that changes in vascular resistance could be assessed indirectly by measurement of limb blood flow and this was subsequently confirmed by Amery *et al.* (1969) and Takeshita & Mark (1980). It is therefore appropriate to assess the effects different antihypertensive agents may have on limb blood flow and vascular resistance during treatment. Further, such measurements may be useful in predicting the effects of antihypertensive agents on the lower limb circulation in patients with hypertension complicated by peripheral vascular disease (McSorley & Warren, 1978; Lepäntalo, 1984). Changes in limb blood flow may be a direct consequence of alteration in vascular resistance, a change in cardiac output (C.O.) or both. In studies designed to measure such changes it is therefore appropriate to also monitor changes in left ventricular stroke volume (SV) and heart rate (HR) during treatment.

There is controversy in the literature as to the effect β-adrenoceptor blockade has on limb blood flow in hypertensive patients, and further, whether ancillary properties such as cardioselectivity, partial agonist activity and the combination of α-/β-adrenoceptor blockade confer any benefit on blood flow (Atterhög *et al.*, 1976, 1977; McSorley & Warren, 1978; Bahlmann *et al.*, 1979; Vandenburg, 1982; Halperin *et al.*, 1986) or may in fact be detrimental (Trap-Jensen *et al.*, 1975; Hartling *et al.*, 1980; Rieckert *et al.*, 1982; Smith & Warren, 1982; Lepäntalo & Totterman, 1983; Johnston *et al.*, 1986). Angiotensin converting enzyme (ACE) inhibitors have recently gained increased popularity in the treatment of hypertension and such drugs should help to preserve limb blood flow as they reduce total peripheral resistance (Fagard *et al.*, 1982). Unlike vasodilators however they do not cause reflex tachycardia and may actually reduce the heart rate (Imai *et al.*, 1982) via increased parasympathetic (Sturani *et al.*, 1982; Ajayi *et al.*, 1985) and/or impaired sympathetic activity (Degli Esposti *et al.*, 1981). The latter could alter cardiac output which some investigators have shown to be decreased during treatment with captopril (Omvik & Lund-Johansen, 1984). Such changes may impair limb blood flow response at rest, during and after exercise (Ferrara *et al.*, 1984).

The aim of this study was therefore to compare the effects of β-adrenoceptor blockers exhibiting differential secondary characteristics with an ACE inhibitor during treatment of hypertension, with reference to potential changes in limb blood flow, heart rate and left ventricular function. The agents chosen were atenolol (a cardioselective β-adrenoceptor blocker), pindolol (a β-adrenoceptor blocker with partial agonist activity), labetalol (a combined α-/β-adrenoceptor blocker) and captopril.

Methods

Forty Caucasian patients (22 male; 18 female; mean age 48.4 years) with asymptomatic and previously untreated essential hypertension (supine phase V diastolic BP, 100–115 mmHg) were recruited and randomized in a single-blind study involving drug treatment with atenolol, labetalol, pindolol or captopril for 7 months. No other anti-hypertensive drugs were taken during the study. After 1 month of matched placebo treatment, active therapy was initiated with atenolol 50 mg nocte, labetalol 100 mg twice daily, pindolol 5 mg twice daily or captopril 12.5 mg twice daily (week 0). Doses of the individual agents (dose ranges: atenolol 50–100 mg once daily; labetalol 100 mg twice daily – 400 mg twice daily; pindolol; 5 mg twice daily – 15 mg twice daily; captopril 12.5 mg twice daily – 50 mg twice daily) were subsequently adjusted by an independent physician at monthly intervals with the aim of achieving a supine (phase V) diastolic BP less than 90 mmHg or a 15% fall in mean blood pressure (MBP) from the pretreatment value. The most commonly prescribed total daily doses at the end of week 24 were atenolol 100 mg, labetalol 400 mg, pindolol 20 mg and captopril 50 mg.

Investigations were carried out at entry to the study (week −4), during and at the end of the placebo phase (weeks −2,0) and at the end of weeks 2, 4, 8 and 24 of active therapy. Patients fasted overnight and took their morning medication as usual. All tests were carried out at the same time of day in a temperature controlled cardiovascular laboratory (25° C). Patients were allowed to acclimatize to the room temperature for half an hour beforehand and wore shorts and short-sleeved shirts for the study.

Investigations were performed by independent observers (D.H.R. and Y.T.) with the patients supine and comprised measurement of:

1. Blood pressure using a random-zero sphygmomanometer. MBP (mmHg) was

calculated as the sum of diastolic blood pressure and one third of the pulse pressure.

2. Heart rate measured from an electrocardiographic tracing (mean of five R-R intervals).
3. Forearm (FBF) and calf (CBF) blood flow by the technique of venous occlusion plethysmography using mercury-in-Silastic strain gauges (Greenfield *et al.*, 1963; Fentem & Greenfield, 1968; Summer, 1982). This method has been shown by us to be reliable, reproducible and useful when serial measurements are required (Roberts *et al.*, 1986). FBF and CBF were expressed as ml blood 100 ml^{-1} tissue min^{-1}. Forearm (FVR) and calf vascular resistance (CVR) were calculated by dividing MBP by limb blood flow and expressed as mmHg ml $blood^{-1}$ 100 ml^{-1} tissue min^{-1}.
4. Left ventricular stroke volume and ejection fraction (EF) derived from internal diameters of the left ventricle in diastole and systole. These were measured from m-mode echocardiograms recorded on paper at 50mm s^{-1} using an ATL. Cardiac Ultrasonic System. Patients were studied in the right anterior oblique position with the transducer always placed in the same intercostal space. All patients selected showed simultaneous visualization of the endocardial surface of the interventricular septum (IVS) and the posterior left ventricular wall (PVW), at or just below the tips of the mitral leaflets. All echocardiograms were analysed 'blind' by an independent observer with coefficients of reproducibility of less than 10% for each parameter assessed. End-diastolic dimension (EDD) was measured from the R wave on the electrocardiogram; end-systolic dimension (ESD) was measured at the minimal vertical distance between IVS and PVW surfaces ['leading edge' technique] (Feigenbaum, 1986). Measurements were taken at end-expiration and the mean values from five cardiac cycles taken. End-diastolic (EDV) and end-systolic (ESV) volumes were derived using the correction factor of Teicholz *et al.* (1976). CO (1 min^{-1}) was derived from the product of SV (ml) and HR.

All investigations were performed at rest and precisely between 2–3 min after exercise on an ergometer bicycle (Paulsen *et al.*, 1979; Roberts *et al.*, 1986). The bicycle load was adjusted to produce a heart rate of 70% of the predicted maximum for age after an initial training period. The same load for each patient was then used throughout the study.

The data were subjected to analysis of covariance for a repeated measures design followed, where appropriate, by Student's *t*-tests. For each haemodynamic parameter, the values recorded on entering the study (week −4) have been used as covariate in the analysis of that parameter. Thus, in the analysis, the covariate has been used to account for the variation due to differences between patients on entering the study. All other measurements, including those before active treatment began, have been included in the analysis producing adjusted values ('cell means') which have variation due to the covariate removed. Statistical analysis was not performed on 'derived' data from haemodynamic parameters already receiving analysis, i.e. FVR, CVR and CO.

The trial was approved by the Ethics Committee of the Royal Liverpool Hospital and the patients informed written consent was obtained.

Results

Of the 40 patients who entered, 37 patients completed the whole study. One patient taking labetalol was withdrawn after 2 weeks of active therapy due to shortness of breath. No other significant adverse drug reactions were noted during the study. Two patients moved to different parts of the country and were lost to follow up after 3 (captopril) and 4 months (pindolol) of active therapy respectively. Results from these two patients are included in the analysis. Patient characteristics are summarized in Table 1.

Data are presented (a) in Tables 2 and 3 as mean values ± s.e. mean for each treatment group at weeks −4 and 24; (b) as figures in graphical form depicting comparisons between and within patient treatment groups with respect to time in the study. Each graph shows the mean for each treatment group at week −4 (the covariate) and for all other line points, the adjusted cell means. Standard error bars are not included in the graphs, since they do not represent the error terms needed in the analysis of covariance.

Blood pressure (Tables 2 and 3; Figure 1)

All active treatments induced a significant fall in BP within 2 weeks of the start of active therapy ($P \leq 0.01$) with no difference between the treatments. In spite of adjustment of dosages there was little additional antihypertensive response by the end of the study.

Table 1 Some characteristics of the study population (mean ± s.e. mean)

	M/F	*Smokers*	*Age, mean range (years)*	*Body weight (kg)*	*Pretreatment supine BP (Phase V diastolic)*
Atenolol	3/7	5	48 ± 4	70.0 ± 3.3	165.5 ± 5.5/101.4 ± 1.9
Captopril	5/5	4	44 ± 3	77.1 ± 3.9	154.8 ± 3.7/102.7 ± 2.6
Labetalol	7/3	5	49 ± 3	76.7 ± 4.0	170.8 ± 5.0/107.9 ± 2.3
Pindolol	7/3	5	51 ± 3	72.2 ± 3.8	173.8 ± 8.9/109.8 ± 2.1

Heart rate (Tables 2 and 3)

Resting HR was reduced more by atenolol and labetalol than by pindolol ($P \leq 0.01$). Captopril caused a small reduction in resting HR (NS). All treatments however significantly reduced the increase in HR following exercise ($P \leq 0.01$). Although pindolol showed the smallest exercise induced HR increase and captopril the largest, the differences were not significant

Forearm and calf blood flow/vascular resistance

Rest (Table 2; Figures 2 and 3) All treatments caused a fall in FBF ($P \leq 0.01$) and CBF ($P \leq 0.01$). There was no change in FVR during the study but this was lower in the captopril group throughout. CVR was higher in the pindolol group throughout the study. Following active treatment there was an increase in CVR in the atenolol group, no change in the labetalol group and a decrease in the pindolol and captopril groups.

Post-exercise (Table 3; Figure 4) Prior to treatment and following placebo therapy CBF showed a mean increase of 26.5% from the resting value measured between 2–3 min after submaximal exercise. All active treatments however caused a smaller increase ($P \leq 0.01$) with no significant differences between them. The associated reduction in CVR was maintained in the patients treated with captopril but was impaired in the atenolol, labetalol and pindolol groups.

Left ventricular stroke volume and ejection fraction (Tables 2 and 3; Figures 5 and 6)

There was no significant change in values for SV and EF at rest and following exercise, within or between treatment groups, following the start of active therapy.

Cardiac output (Tables 2 and 3)

Active therapy with atenolol and labetalol caused a fall in resting CO whereas pindolol and captopril produced little change. Following exercise all active treatments caused a reduction in CO but this was greatest with labetalol and least with captopril.

Discussion

The haemodynamic mode of action of β-adrenoceptor blockers in the treatment of hypertension is far from uniform as would be expected of members of the same drug class. While non-selective (e.g. propranolol) and cardioselective compounds both reduce cardiac output and increase total peripheral resistance (Weil & Waite, 1982), the latter may cause a smaller reduction in limb blood flow by not affecting β_2-adrenoceptors in blood vessels (McSorley & Warren, 1978). Those exhibiting intrinsic sympathomimetic activity (Atterhög *et al.*, 1977) or combination with α-adrenoceptor blockade (Halperin *et al.*, 1986), however tend to lower peripheral resistance whilst having little effect on cardiac output. Although these differences are more pronounced at rest than during exercise they may help to preserve limb blood flow (Smith & Warren, 1982). Captopril has been shown to preserve or even increase limb blood flow measured at rest and during reactive hyperemia by reduction of peripheral vascular resistance (Novo *et al.*, 1982; Strano *et al.*, 1982). There is little information on limb blood flow after exercise however and its putative anti-sympathetic activity questions its ability to preserve flow in this situation.

We have performed a single-blind 'parallel groups' study to compare the effects of atenolol, labetalol, pindolol and captopril on limb blood flow, heart rate and left ventricular function over a 6 month period. Although not placebo controlled and double-blind this design permits assessment of short and long term haemodynamic changes within and between patient groups with all measurements/calculations performed by an independent 'blind' observer. The number of patients studied was determined from power calculations with the aim of detecting a significant change of 0.5 ml 100 ml^{-1} min^{-1} in limb

Table 2 Effect of antihypertensive agents on haemodynamics at rest (mean values ± s.e. mean)

	Atenolol		*Captopril*		*Labetalol*		*Pindolol*	
Week	*–4*	*24*	*–4*	*24*	*–4*	*24*	*–4*	*24*
MBP (mm Hg)	122.0 ± 3.8	103.5 ± 3.9	118.1 ± 1.2	99.4 ± 2.0	128 ± 3.0	110.8 ± 4.9	132.5 ± 4.3	109.0 ± 2.9
HR (beats min^{-1})	75.2 ± 2.9	62.4 ± 2.1	79.6 ± 3.5	73.3 ± 3.2	83.8 ± 3.5	66.2 ± 1.7	76.4 ± 3.4	71.5 ± 1.3
FBF (ml 100 ml^{-1} min^{-1})	4.2 ± 0.3	3.5 ± 0.4	5.1 ± 0.5	4.1 ± 0.3	4.1 ± 0.5	3.3 ± 0.3	3.9 ± 0.3	3.3 ± 0.2
FVR (mm Hg ml^{-1} 100 ml^{-1} min^{-1})	30.6 ± 2.6	33.8 ± 3.8	25.7 ± 3.1	25.6 ± 1.4	34.3 ± 3.3	35.4 ± 3.6	36.5 ± 3.6	35.4 ± 3.5
CBF (ml 100 ml^{-1} min^{-1})	3.4 ± 0.3	2.6 ± 0.3	3.5 ± 0.4	3.2 ± 0.2	3.9 ± 0.3	3.5 ± 0.5	3.0 ± 0.3	2.7 ± 0.2
CVR (mm Hg ml^{-1} 100 ml^{-1} min^{-1})	38.1 ± 3.4	43.2 ± 4.5	37.5 ± 4.4	32.5 ± 2.3	34.3 ± 2.2	35.8 ± 4.9	47.7 ± 4.9	41.5 ± 4.0
SV (ml)	75.0 ± 5.3	78.5 ± 4.1	70.0 ± 3.9	72.5 ± 5.1	80.9 ± 3.8	84.5 ± 5.5	80.1 ± 6.0	82.5 ± 6.3
EF (%)	81.8 ± 2.8	81.1 ± 1.8	78.6 ± 2.1	74.2 ± 2.2	76.6 ± 1.9	75.7 ± 3.1	75.4 ± 2.9	71.5 ± 2.2
CO (l min^{-1})	5.6 ± 0.4	4.9 ± 0.5	5.6 ± 0.4	5.3 ± 0.3	6.7 ± 0.5	5.6 ± 0.3	6.1 ± 0.4	5.9 ± 0.4

Table 3 Effect of antihypertensive agents on haemodynamics 2–3 min after exercise (mean ± s.e. mean)

	Atenolol		*Captopril*		*Labetalol*		*Pindolol*	
Week	*–4*	*24*	*–4*	*24*	*–4*	*24*	*–4*	*24*
MBP (mm Hg)	121.3 ± 4.2	102.6 ± 3.8	118.0 ± 2.1	99.4 ± 2.4	126.8 ± 2.7	111.4 ± 3.9	128.2 ± 3.7	109.6 ± 3.1
HR (beats min^{-1})	97.4 ± 2.9	75.6 ± 3.9	102.8 ± 3.8	92.9 ± 5.1	102.8 ± 2.4	77.6 ± 3.2	98.6 ± 2.2	76.3 ± 2.5
CBF (ml 100 ml^{-1} min^{-1})	4.0 ± 0.3	3.2 ± 0.3	4.6 ± 0.4	3.8 ± 0.4	5.1 ± 0.4	4.1 ± 0.4	3.8 ± 0.3	2.8 ± 0.2
CVR (mm Hg ml^{-1} 100 ml^{-1} min^{-1})	31.2 ± 1.9	34.5 ± 3.3	27.0 ± 2.2	28.3 ± 2.9	26.2 ± 1.9	31.1 ± 4.7	35.9 ± 3.1	40.9 ± 4.5
SV (ml)	85.3 ± 5.5	88.1 ± 4.3	91.0 ± 8.4	88.0 ± 7.3	94.1 ± 8.0	95.5 ± 7.5	91.0 ± 5.9	98.5 ± 7.5
EF (%)	82.8 ± 2.4	81.1 ± 1.8	82.4 ± 1.5	76.3 ± 2.9	82.9 ± 1.2	79.1 ± 2.4	73.4 ± 2.1	71.5 ± 2.2
CO (l min^{-1})	8.3 ± 0.6	6.7 ± 0.5	9.3 ± 0.6	8.2 ± 0.7	9.7 ± 0.7	7.4 ± 0.7	9.0 ± 0.5	7.5 ± 0.6

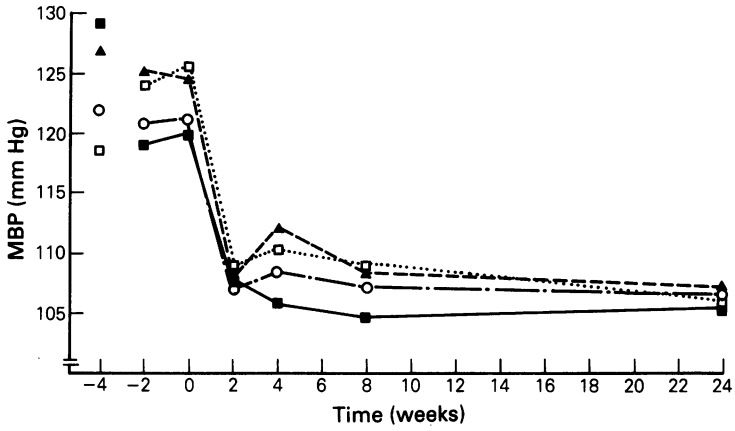

Figure 1 The effects of atenolol (○), captopril (□), labetalol (▲) and pindolol (■) on resting mean blood pressure.

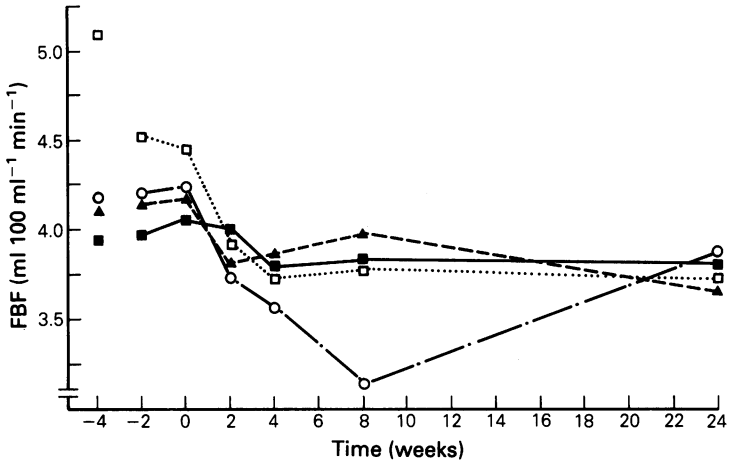

Figure 2 The effects of atenolol (○), captopril (□), labetalol (▲) and pindolol (■) on resting forearm blood flow.

blood flow. This was based on values for a Type I (α) and Type II (β) error both being 0.05 with a standard deviation of 0.3 ml 100 ml^{-1} min^{-1} for repeated measurement of limb blood flow. The minimal required number of patients on each treatment was thus calculated as 9.4 (Pocock, 1984).

All four treatments induced a significant fall in blood pressure within 2 weeks of the start of active treatment and there were no differences between the treatments in terms of control of blood pressure. All four groups of patients were sensitive to small doses of the individual antihypertensive agents with little additional hypotensive effect produced by increasing dosage. The data are insufficient to state that these agents showed a flat dose response relationship, however, as most patients only received one dose increment on active therapy.

The results of this study demonstrate that all four drugs reduce resting and post-exercise limb blood flow despite differing modes of action as antihypertensive agents. We have shown no change in FVR within patient groups but have demonstrated differential changes in CVR with the individual agents at rest and after exercise. The reduction in CVR with pindolol and captopril has not served to maintain limb blood flow during blood pressure reduction however. Blood flow in a tissue is determined by the

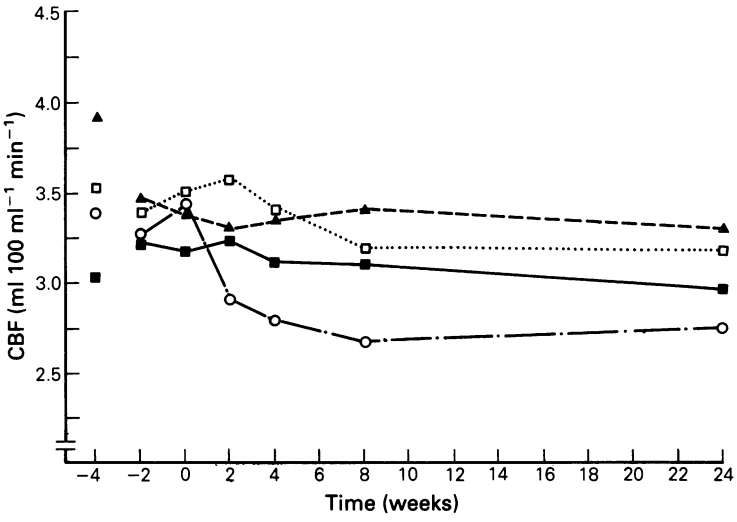

Figure 3 The effects of atenolol (○), captopril (□), labetalol (▲) and pindolol (■) on resting calf blood flow.

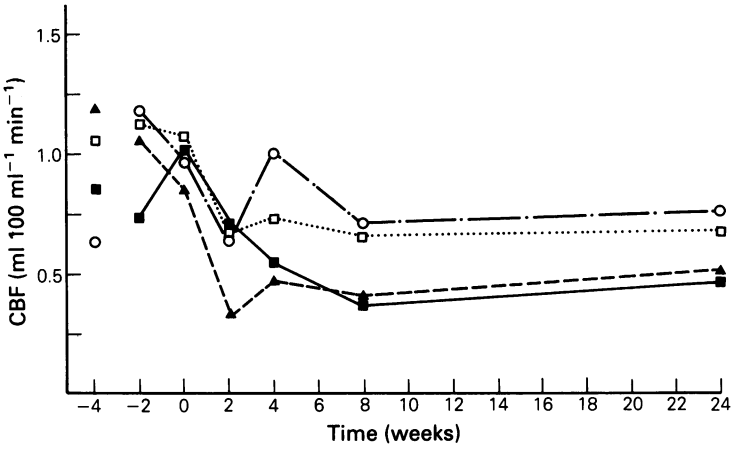

Figure 4 The effects of atenolol (○), captopril (□), labetalol (▲) and pindolol (■) on changes in post-exercise calf blood flow.

perfusion pressure (arterial blood pressure minus venous blood pressure) and blood flow resistance in the tissue

$$[\text{Blood flow} \simeq \frac{\text{Perfusion pressure}}{\text{Resistance}}]$$

(Folkow, 1964; Sivertsson, 1979). The reduction in flow (mainly to skeletal muscle) therefore appears to be a consequence of reduced perfusion pressure. Although skeletal muscle shows a moderate degree of autoregulatory ability to maintain limb blood flow in normotensives this does not appear sufficient for the hypertensive population during treatment with the agents studied. It is of note that the fall in limb blood flow was maintained at the end of 6 months treatment. It seems unlikely therefore that there is significant alteration in baroceptor activity at this time using these antihypertensive agents.

This study has also demonstrated all four antihypertensive agents to reduce resting and post-exercise heart rate. While resting rates showed a greater decrease on treatment with atenolol and labetalol ($P \leq 0.01$) there was no significant

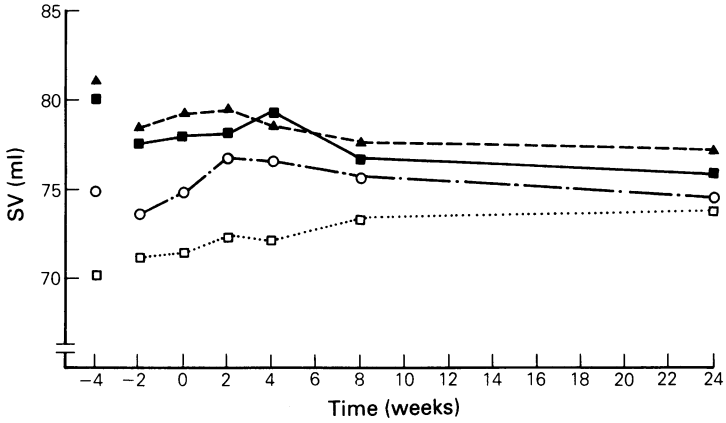

Figure 5 The effects of atenolol (○), captopril (□), labetalol (▲) and pindolol (■) on resting stroke volume.

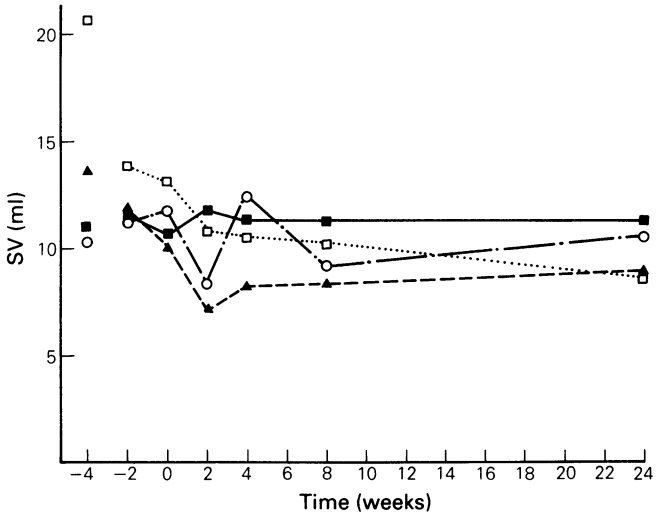

Figure 6 The effects of atenolol (○), captopril (□), labetalol (▲) and pindolol (■) on changes in post-exercise stroke volume.

difference in the magnitude of decrease in heart rate after exercise between the four treatments. The reduction on captopril however was clearly less than with the other three drugs and may reflect a Type II error. The relative reductions of resting rate with atenolol, labetalol and pindolol clearly reflect the influence of β-adrenoceptor blockers with secondary characteristics of cardioselectivity, combined α-adrenoceptor blockade and intrinsic sympathomimetic activity. The approximately equal reductions in post-exercise values on these three drugs strongly suggest that such differential effects on heart rate are lost during and after exercise.

Captopril has previously been shown to reduce resting heart rate due to enhanced parasympathetic tone (Campbell *et al.*, 1985; Ajayi *et al.*, 1985). The additional reduction in post-exercise heart rate is in contradiction to the belief that captopril does not alter sympathetic tone or sympathetically mediated reflexes (Niarchos *et al.*, 1982; Zanella *et al.*, 1981). Despite the reductions in heart rate with the four agents we observed no compensatory increase in left ventricular stroke volume or ejection fraction. We have therefore shown all four agents to also reduce cardiac output consequent to their effects in reducing heart rate. As one of the

cardiovascular changes in untreated hypertension may be an elevated cardiac output (usually as a result of a rise in heart rate), it is possible that captopril as well as β-adrenoceptor blockers may exert a direct effect on this haemodynamic abnormality. It is likely that part of the reduction in perfusion pressure to the limbs may also be related to a fall in cardiac output (Kendall, 1981) which may help to explain the reduction in limb blood flow with the four agents studied. Further similar studies using agents which do not reduce heart rate e.g. nifedipine, would therefore be appropriate to assess the contribution made by altered cardiac output in determining perfusion pressure.

In conclusion we believe that the reduction in limb blood flow with the agents studied appears primarily a consequence of reduced perfusion pressure associated with limited autoregulation of skeletal muscle circulation. Such results may have important implications for patients with hypertension complicated by intermittent claudication.

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